UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,959	10/07/2003	Susan Jane Knox	STAN-274	6076

24353 7590 01/07/2005

BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 01/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/680,959	KNOX ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. code, not included in this action can be found in a prior office action.

The amendment filed on November 29, 2004 has been received, and the amendment to claim 1 has been entered. Claims 3 and 9-11 have been canceled.

Accordingly, claims 1, 2 and 4-8 are examined on the merits herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 4-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing cell death from exposure to ionizing radiation, does not reasonably provide enablement for a method of preventing radiation-induced cell killing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. "Prevention" encompasses stopping all occurrences of cell death, whereas Applicants have demonstrated only a reduction in the relative amount of cell death (see Figs. 2 and 4). One of skill in the art would not expect total elimination of cell death under any radiation conditions.

Further, Figures 2 and 4 show experimental data with two types of normal cells, rat fibroblasts and canine kidney epithelial cells, respectively. The data show that treatment with several doses of valinomycin, 0.01 – 1 micromolar, increases the percentage of cells that survive exposure to gamma radiation, i.e., decreases the relative amount of cell death from gamma radiation exposure. As only two types of cells, three different doses of one hyperpolarizing agent and three different doses of gamma radiation were used, the specification provides only limited information with regard to reducing cell death from radiation exposure. As a result, one of skill in the art would not be able to generalize to the point of being able to predict how much reduction in cell death would be expected when other doses of radiation, other normal cell types, other hyperpolarizing agents or other doses of the same hyperpolarizing agent are used. Certainly, one would not be able to generalize to the level that treatment with a particular dose of a particular hyperpolarizing agent would prevent cell death from exposure to a particular dose of radiation in a particular normal cell type. Thus, a holding of non-enablement is required.

Claim Rejections - 35 USC § 102

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Fox, Pfluegers Archiv 35144):303-314, 1974. Fox discloses a method of protecting normal cells (normal neurons) from radiation damage in which the cells are contacted with a hyperpolarizing agent that is effective in hyperpolarizing the cell membrane. The cells are contacted with a phthalic acid buffer at low pH which stops the Na^+ current and

blocks the Na^+ channels with protons (H^+). A negative holding membrane potential is created, and the membrane is hyperpolarized. The cells are then irradiated with UV radiation, and decreased sensitivity to radiation is measured in cells with proton-blocked Na^+ channels in the nodal membrane (see p. 304, Methods, and pp. 308-311). Thus, a holding of anticipation is required.

All of Applicants' arguments have been considered but are not persuasive of error. Applicants assert that the claimed method differs from that of Fox because Fox relates to photooxidation of the cell membrane and not to hyperpolarization and because the radiation in Fox is UV radiation, not ionizing radiation.

In response to Applicants' argument that the reference fails to show certain features of applicant's invention, it is noted that the features upon which Applicants rely (i.e., photooxidation and UV vs. ionizing radiation) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the method of Fox, and as recited in the claims, cell membranes are exposed to a hyperpolarizing agent, to hyperpolarize the ion channels in the membrane. The cells are then exposed to radiation. Hyperpolarization is found to have a protective effect on the cell membrane. Whether or not photooxidation occurs is not a limitation recited in the claims. Additionally, the claims recite "radiation exposure" and "radiation damage." UV radiation is also a type of radiation in the electromagnetic spectrum. Thus, the rejection of record must be maintained.

Claim Rejections - 35 USC § 103

Claims 1, 2 and 4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gilbert et al., J Cellular Physiology 168:1 14-122, 1996. Gilbert discloses a method of protecting cells from radiation damage in which the cells are contacted with a hyperpolarizing agent that is effective in hyperpolarizing the cell membrane. The cells are transfected with an expression vector containing the Bcl-2 gene, effecting expression of the Bcl-2 gene which hyperpolarizes the membrane, or the cells are contacted with valinomycin. Valinomycin opens the K^+/ATP channels, which hyperpolarizes the membrane. The cells are then irradiated, and improved viability is measured in cells treated with either the Bcl-2 expression vector and/or valinomycin. (see p. 115, paragraphs entitled Cell lines and cell culture and Effect of valinomycin on cell viability and membrane potentials, and p. 116, 2^d paragraph under Effect of Bcl-2 on radiosensitivity and paragraph entitled Exposure of cells to valinomycin). Gilbert, however, discloses treating the PW and HL60 cell lines, a human B cell lymphoma line and a human leukemia cell line, respectively, and does not disclose treating normal cells. But, Gilbert teaches that hyperpolarizing agents act on the K^+/ATP channels in cell membranes (see p. 118, paragraph entitled Exposure to ouabain) and does not indicate that there are any differences in the K^+/ATP channels between normal cells and PW or HL60 cells. Therefore, one of ordinary skill in the art would have expected, with a reasonable degree of success, that treating normal cells with a hyperpolarizing agent would provide the same protection from radiation as treating PW or HL60 cells. As a

result, the skilled artisan would have been motivated to modify the teachings of Gilbert to apply the method to normal cells for the treatment benefits disclosed in the reference (improved radiation resistance). Thus, a holding of obviousness is required.

All of Applicants' arguments have been considered but are not persuasive of error. Applicants assert that the claimed method differs from that of Gilbert because Gilbert uses cell lines established from cancer cells and not normal (untransformed) cells. Applicants note that in cancerous cells, the cell cycle is regulated differently than in normal cells. Applicants also assert that, as disclosed in Williams et al., Cancer Res 60:4358-4361, 2000, most tumor cells express high levels of Bcl-2, which leads to up-regulation of the channels that pump Ca^{2+} ions into cells. Baseline activity of the K^{+}/ATP channels is also increased.

In response to Applicants' argument that the references fail to show certain features of Applicant's invention, it is noted that a feature upon which Applicants rely (i.e., cell cycle regulation) is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. Moreover, similarly to Gilbert, the Williams reference teaches that the membranes of cancer cells are hyperpolarized, due to hyperpolarization of the Ca^{2+} channels, from increased expression of Bcl-2, a hyperpolarizing agent. Williams also teaches that the activity of K^{+}/ATP channels in cancer cells is increased relative to the activity in normal cells.

Nevertheless, Williams does not indicate the degree to which K^+/ATP channel activity is increased, and this is also an activity present in normal cells. Apart from increased activity, there is no indication that the K^+/ATP channels of cancer cells are different from those in normal cells. Although normal cells and cancer cells may differ in certain respects, such as cell cycle regulation, because both types of cells require K^+/ATP channels to remain viable, one of ordinary skill in the art would have expected that an agent that hyperpolarized the K^+/ATP channels of cancer cells would also have hyperpolarized the K^+/ATP channels of normal cells. Thus, the rejection of record must be maintained.

No claim is allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner
Art Unit 1651

rk
2005-01-04

FRANCISCO PRATS
PRIMARY EXAMINER